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An alternative to steroids for prevention of respiratory distress syndrome (RDS): multicenter controlled study to compare ambroxol and betamethasone

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1 Introduction

The respiratory distress syndrome (RDS) continues to rank as a major cause of mortality among non-malformed infants. Even when it is not fatal, the disease may have late sequelae, involving mainly the central nervous system (CNS) and the cardiopulmonary apparatus. The incidence of RDS is inversely correlated with gestational age. Its cause is the insufficient production of substances that lower surface tension (surfactants) in fetal lungs.

The experience of LIGGINS and HOWIE [7] with antenatal maternal administration of steroids for prevention of RDS led to widespread adoption of this preventive approach. Further studies substantially confirmed the effectiveness of the steroids but also brought to light several conditions in which the benefit was slight or nil [1, 2, 4, 11].

These conditions include: 1) treatment to delivery time less than 24 hours and more than one week, 2) gestational age less than 30 and more than 34 weeks, 3) rupture of membranes (ROM) more than 48 hours prior to delivery, 4) male sex, 5) white race, 6) multiple pregnancy, and 7) fetal acidosis.

Furthermore steroids have potential maternal, fetal and neonatal adverse effects [4, 16, 17, 19], among which the most dangerous is probably the increased incidence of neonatal infection, to which preterm infants are already more susceptible. The percentage of deaths due to infection within 28 days of birth was higher and polymorphonuclear leukocytes (PMNL) functions were reduced in infants whose mothers had received steroids for prevention of RDS than in those whose mothers had not been treated [5].

All this has encouraged attempts to find alternative treatments of at least equal efficacy but without adverse reactions. Many substan-

Curriculum vitae

Dr. MASSIMO LUERTI *was born in Milan on 1946. He took the degree in Medicine in 1970 and the speciality in Obstetrics and Gynecology in 1974. He is author or co-author of 93 scientific publications about arguments of perinatal medicine as well as of gynecologic oncology and contraception. He is a fellow of the Italian Society of Obstetrics and Gynecology as well as of the Italian Society of Perinatal Medicine. He is co-editor of the volumes "New trends in fetal lung immaturity" and "Diagnosis and treatment of fetal lung immaturity".*

ces have been held to be capable of stimulating surfactant production: aminophylline, thyroid hormones, cyclic-AMP, ethanol, fibroblast-pneumocyte factor, bromhexine and others. None of them – for various reasons – has been accepted as a true alternative to steroids.

A series of experimental data have demonstrated that ambroxol, a benzylamine, stimulates surfactant production and secretion by type II pneumocytes, even though the mechanism of action is not yet fully understood.

The most important experimental findings are that ambroxol:

1) increases surfactant phospholipids concentrations in the amniotic and fetal tracheal fluid [3, 10];
2) stimulates the development of intracellular organelles involved in the surfactant secretion process [18];
3) increases pulmonary compliance in the rabbit neonate [12]. Ambroxol readily crossess the placental barrier and concentrates electively in the fetal lungs and liver [13];
4) and it has been demonstrated that ambroxol lowers the incidence of RDS in preterm infants born of treated mothers compared to mothers given placebo [8, 20].

The aim of this study was to evaluate the effectiveness of ambroxol versus the steroids in reducing the incidence of RDS in preterm newborns with particular regard to the occurrence of neonatal infection.

2 Materials and methods

Starting in September 1981, we organized a randomized multicenter trial in which four centers in the Lombardy region and two centers in other regions took part.

Women at 27 to 34 weeks' gestation with threatened premature or planned premature labor were admitted into the trial.

Criteria for exclusion were:

1) Delivery expected within 24 hours;
2) More than two weeks disagreement in assessing gestational age using patient's history data and ultrasound data;
3) Severe hypertension (B. P. more than 160/100 mmHg);
4) Class-B-R diabetes;
5) Hyperthyroidism;
6) Drug addiction with heroin up to the third trimester of pregnancy;
7) Previous treatment during pregnancy with drugs enhancing fetal lung maturity.

Tocolysis with a beta-mimetic agent was allowed to delay labor.

Consenting patients admitted to the trial were randomly treated, on the basis of chance number tables, with betamethasone or ambroxol. The study was stratified with separated randomization for each center and accurate control was performed on correct use of random tables. The betamethasone group received 6 mg of betamethasone phosphate and 6 mg of betamethasone acetate intramuscularly, and the dose was repeated 24 hours later. The ambroxol group received the drug diluted in 500 ml saline as a slow intravenous infusion according to a long regimen (1 g/day for 5 days) or a short regimen (1 g every 12 hours for 4 times). The two ambroxol dosage regimens were chosen freely in relation to the expected delay of labor. Because of different route and frequency of administration of the two drugs a blinded study was too complicated to be performed.

The diagnosis of RDS was based on the existence of one or more of both clinical and radiological signs given in table I and its severity was rated according to the gas-analytical criteria shown. The diagnosis of maternal puerperal infection was based upon either the finding of a skin temperature more than 38 °C on two occasions (temperatures beeing measured at least every 6 hours), or a clinical evaluation consistent with endometritis or wound infection. The diagnosis of neonatal infection was based upon clinical and radiological criteria and confirmed by a positive culture.

Evaluation of maternal and neonatal infection rate was performed in infants born at each gestational age only in the four Lombardy regional centers, owing to reasons of organization. Neonatal pathology was reviewed in all

Table I. Criteria for diagnosis of RDS.

RDS defined by the presence of:	
Beginning before 4 hours of life	
Duration more than 24 hours	
Clinical signs (one or more):	Respiratory rate >60/min Intracostal retractions Flaring of the alae nasi Grunting on expiration Cyanosis in room air with falling in PO_2 below 60 mmHg
Radiological signs:	Thoracic roentgenogram showing reticulogranular pattern and/or air bronchograms

Severity was defined as:
- Mild: if arterial or $tcPo_2$ 50–80 mmHg with room $FiO_2 \leqslant 0.3$
- Moderate: if arterial or $tcPo_2$ 50–80 mmHg with FiO_2 between 0.4. and 0.6. → c PAP
- Severe: if arterial or $tcPo_2$ mmHg < 50 or Pco_2 > 60 with FiO_2 between 0.4 and 1 → assisted ventilation.

cases by a neonatal coinvestigator who was blinded as to the treatment. All data were checked and analyzed with an Apple II computer at the IVth Department of Obstetrics and Gynecology of the University of Milan, L. Sacco Hospital. Statistical analyses were by Student's t-test and the chi-square test.

3 Results

As of November 15, 1984, 288 randomized patients had delivered 315 neonates. Thirty-eight patients were excluded because of either the presence of criteria for exclusion or procedural errors. There were 2 stillbirths. Ninety-nine neonates were born after the 37th week of pregnancy. 7 died of other causes within the first 3 hours of life before the onset of RDS could be established. The incidence of RDS was assessed in 169 viable neonates born before the 37th completed week of gestation (259 days of amenorrhea). Of these, 86 were born from 76 mothers treated with betamethasone and 83 from 76 mothers treated with ambroxol (table II).

All the betamethasone patients completed one course of treatment, whereas 14 of the ambroxol group (18%) received less than the scheduled number of doses because of onset of labor. Comparison of the mothers in the two groups showed no significant differences in the main maternal factors affecting the development of RDS (table III). The two groups of mothers were also compared as to use of beta-

Table II. Study population.

	Groups			
	Betamethasone		Ambroxol	
	Mothers	Infants	Mothers	Infants
Total randomized	129	144	159	171
Excluded from the study	21	22	15	16
Fetal deaths	1	1	1	1
Liveborn after the 37th week	29	33	62	66
Early neonatal death before RDS assessment	2	2	5	5
Available for RDS assessment	76	86	76	83

Table III. Characteristics of treatment groups (mothers)[1].

Characteristic	Groups	
	Betamethasone (n = 76)	Ambroxol (n = 76)
Gestational age at delivery mean ± S.D. (days)	229.0 ± 17.2	231.9 ± 13.8
⩽ 34 weeks (%)	53 70%	52 68%
> 34 weeks (%)	23 30%	24 32%
Treatment to delivery time mean ± S.D. (days)	14.1 ± 15.9	11.4 ± 12.9
ROM to delivery time mean ± S.D. (hours)	27.3 ± 15.4	26.9 ± 17.6
Multiple pregnancy (%)	10 13%	7 9%
Cesarean section (%)	32 42%	33 43%
Placenta previa (%)	4 5%	2 3%

[1] Statistical analysis. The difference between the two groups was not significant for any of the recorded characteristics.

mimetic agents, and no significant difference was found (table IV). There was no significant difference between the two groups of neonates as regards main neonatal factors affecting the development of RDS (table V). The overall incidence of RDS was higher in the betamethasone group (31%) than in the ambroxol group (13%) as was the incidence of mild, moderate, severe and fatal RDS. The difference was significant ($P < 0.05$) (table VI).

The incidence of RDS was generally higher in the betamethasone group vs ambroxol group in five centers (29% vs 13%, 40% vs 10%, 35% vs 15%, 29% vs 13%, 24% vs 8%), whereas in one group it was comparable (13% in the betamethasone group vs 14% in the ambroxol group).

The incidence of RDS in neonatal subgroups divided on the basis of twin births, gestational age, ROM to delivery time, treatment to delivery time and sex of the newborn was in every case higher in the betamethasone group. The difference was significant in twin births, when delivery was prior to the 31st week, when ROM occurred more than 48 hours earlier, and in female infants. As well as in these conditions, in which steroids are known not to be effective, the difference was significant when the treat-

Table IV. Use of betamimetic drugs[1].

Betamimetic agents	Betamethasone (n = 76)		Ambroxol (n = 76)	
	Cases	(%)	Cases	(%)
None	4	5	5	6
Ritodrine	48	63	50	66
Isoxsuprine	11	14	3	4
Salbutamol	4	5	6	8
More than one drug	9	1	12	16
Mean total dosage (mg)*	494.7 ± 639.1		581.9 ± 835.9	
Mean duration of treatment (days)	8.3 ± 8.7		8.8 ± 10.9	

[1] = Statistical analysis. The difference between the groups was not significant for any of the recorded characteristics.

* = Dosage equalized to ritodrine according to a isoxsuprine/ritodrine dosage ratio of 5:1 and a salbutamol/ritodrine dosage ratio of 1:10.

Table V. Characteristics of treatment groups (infants)[1].

Characteristic	Groups	
	Betamethasone (n = 86)	Ambroxol (n = 83)
Gestational age mean ± S.D. (days)	228.8 ± 17.7	232.5 ± 13.6
⩽ 34 weeks	60 70%	56 68%
> 34 weeks	26 30%	27 32%
Birth weight mean ± S.D. (gm)	1927 ± 540.0	1982 ± 527.0
⩽ 1.500	23 27%	14 16%
> 1.500	63 73%	70 84%
Apgar 1′ (mean ± S.D.)	5.6 ± 2.9	5.9 ± 2.6
Apgar 5′ (mean ± S.D.)	7.2 ± 1.9	7.3 ± 2.0
Twins (%)	20 23%	13 17%

[1] = Statistical analysis. The difference between the groups was not significant for any of the recorded characteristics.

Table VI. Incidence of RDS[1].

RDS		Betamethasone (n = 86)		Ambroxol (n = 83)	
		Cases	(%)	Cases	(%)
RDS	No RDS	59	69	72	87
	Mild	9	10	7	9
	Moderate	7	8	2	2
	Severe	5	6	0	0
	Fatal	6	7	2	2

[1] = Statistical analysis: $X^2 = 11{,}27$ (d.f. = 4) $P < 0.05$

ment to delivery interval was between 2 and 7 days, i.e. the limit within which steroids are effective (table VII).

The incidence of RDS was 15% in neonates whose mothers had been given the long dosage regimen and 12% in neonates whose mothers had been given the short dosage regimen. The difference was not significant.

The infants born in the four Lombardy regional centers included 100 in the betamethasone group and 140 in the ambroxol group. The puerperal infection rate in the mothers of these infants was 33% in the betamethasone group and 36% in the ambroxol group (the difference was not significant). In the same 240 infants, the betamethasone group had a slightly lower gestational age at birth (242 days), a slightly higher treatment to delivery interval (29.3 days) and a slightly higher percentage of cases with ROM >48 hours (24%) than the ambroxol group (246 days, 28.5 days and 19% respectively). Although none of these differences were significant, the neonatal infection rate through the 28th day of life was significantly higher ($P < 0.05$) in the betamethasone group (18% with four fatalities) than in the ambroxol group (9% with one fatality). The infected neonates in the betamethasone group had a significantly lower mean gestational age, significantly shorter mean treatment to delivery interval and a significantly longer ROM to delivery time than the non-infected neonates; whereas, there was no difference between the infected and non-infected neonates in the ambroxol group as regards these three parameters (table VIII). All deaths for infection occurred after the first week of life. The type of infection and the causal agents are listed in table IX.

The perinatal mortality of infants in the trial was 9% (11/122) in the betamethasone group and 8% (13/155) in the ambroxol group; the 28 day neonatal mortality was 12% (14/121) in the betamethasone group and 8% (13/154) in the ambroxol group; both differences were not significant (table X).

Table VII. Incidence of RDS in subgroups (infants).

Subgroups	Betamethasone (n = 86)		Ambroxol (n = 83)		P
	RDS Cases	(%)	RDS Cases	(%)	
Single delivery infants	20/68	29	11/69	16	< 0.01
Multiple delivery infants	7/18	39	0/14	0	
Gestational age					
≤30 weeks	10/12	83	2/ 7	29	
31–34 weeks	13/49	26	6/51	12	< 0.05
>34 weeks	4/25	16	3/25	12	
ROM to delivery time					
≤24 hours	14/49	28	9/60	15	
25–48 hours	0/ 5		0/ 5		< 0.01
>48 hours	13/32	41	2/18	11	
Treatment to delivery time					
< 2 days	5/16	31	3/24	12	
2– 7 days	13/35	37	1/19	5	< 0.01
> 7 days	9/35	26	7/40	17	
Sex					
Female	15/35	43	5/45	11	< 0.01
Male	12/51	23	6/38	16	

Table VIII. Characteristics of infected infants in treatment groups.

Treatment	Infected infants	Non-infected infants	P
Betamethasone group (n = 100)			
Gestational age mean ± S.D. (days)	226.5 ± 23.6	246 ± 23.7	< 0.005
Treatment to delivery time mean ± S.D. (days)	13.5 ± 19.5	33.6 ± 26.7	< 0.005
ROM >48 hours (%)	38	15	< 0.01
Ambroxol group (n = 140)			
Gestational age mean ± S.D. (days)	243.5 ± 17.5	249.2 ± 21.3	> 0.05
Treatment to delivery time mean ± S.D. (days)	20.3 ± 23.8	28.5 ± 22.0	> 0.05
ROM >48 hours (%)	14	27	> 0.05

The mean gestational age at treatment and at delivery, birth weight, Apgar score at 1 and 5 min were significantly lower in RDS than non-RDS cases; however, mean ROM to delivery time, percentage of male sex, incidence of cesarean section and, particularly, use of beta-mimetics and mean treatment to delivery time, which were thought to be more decisive than steroid prevention [15] in reducing the incidence of RDS, were not significantly different in RDS and non-RDS cases (table XI).

The only short-term negative side effects seen in the mothers, the fetuses, or the neonates after ambroxol administration were nausea and headache in about 10% of the mothers.

Table IX. Neonatal infections.

Ambroxol group		Betamethasone group
Etiologic agent	Type of infection and day of onset	Etiologic agent
S. aureus	Subcutaneous abscess (16th)	
	Subcutaneous abscesses (12th)*	S. aureus
	Skin infection (26th)	S. albus
S. albus	Skin infection (10th)	
S. albus	Skin infection (13th)	
S. albus	Skin infection (14th)	
S. albus	Skin infection (15th)	
Candida sp.	Oral moniliasis (12th)	
Candida sp.	Oral moniliasis (17th)	
Candida sp.	Oral moniliasis (10th) °	
	Oral moniliasis (12th)	Candida sp.
	Oral moniliasis (14th)	Candida sp.
	Oral moniliasis (4th)	Candida sp.
E. coli	UTI (11th)	
E. coli	UTI (16th)	
E. coli	UTI (25th) °	
	UTI (4th)	Enterobacter
	UTI (26th)	Proteus sp. + K. pneumoniae
	UTI (12th)	Proteus sp.
	UTI (10th)	E. coli
	UTI (27th)	E. coli
	UTI (20th)	K. pneumoniae
	Pneumonia (2nd)†	P. aeruginosa + E. coli
	Pneumonia (5th)†	Pseudomonas sp.
	Pneumonia (11th)†	Pseudomonas sp.
Pseudomonas sp.	Pneumonia (2nd)	
K. pneumoniae	Sepsis (12th)†	
	Sepsis (22nd)†	S. marcescens + P. aeruginosa
	Conjunctivitis (2nd)*	E. coli
	Conjunctivitis (18th)	P. aeruginosa
	Otitis media (16th)	S. aureus
	Omphalitis (7th)	Proteus mirabilis + S. epidermidis
Streptococcus spp.	Pharyngitis (3rd)	
Morbidity rate = 9% (13/140)		Morbidity rate = 18% (18/100)
Mortality rate = 0.7% (1/140)		Mortality rate = 4% (4/100)

° Associated moniliasis and UTI (urinary tract infection)
* Associated conjunctivitis and subcutaneous abscesses
† Death

Table X. Fetal and neonatal deaths*.

Betamethasone group				Ambroxol group			
Cause of death	Sex	Gestational age (week)	Birth weight (g)	Cause of death	Sex	Gestational age (week)	Birth weight (g)
1-RDS	M	32.5	2015	1-RDS	M	29.3	1030
2-RDS	M	29.0	1190	2-RDS	M	32.0	1540
3-RDS	M	27.6	1080	Infection			
4-RDS	F	32.5	1900	3-Sepsis	M	33.5	1520
5-RDS	M	31.3	1500				
6-RDS	F	29.2	950	Miscellaneous			
Infection				4-Intrauterine hypoxia	M	36.3	2110
7-Sepsis	M	26.2	970	5-Multiple malformation	M	34.4	1560
8-Pneumonia	F	29.2	1260	6-Intrauterine hypoxia	F	34.0	3300
9-Pneumonia	M	29.2	1240	7-Sudden death-apnea	M	28.4	1050
10-Pneumonia	M	30.5	1090	8-Hydrops	F	29.0	1800
Miscellaneous				9-Rh immunization	M	32.4	1950
11-Potter's syndrome	M	33.4	1100	10-Hydrops	F	34.1	2420
12-Cord prolapse	M	38.4	3500	11-Hydrops	M	35.0	2510
13-Intracranial hemorrhage	F	33.0	1300	12-Intrauterina hypoxia	M	34.0	1900
14-Congenital syphilis	M	32.6	1660	13-Multiple malformation	M	32.3	1880
15-Stillbirth				14-Stillbirth			

* All diagnosis were made on the basis of autopsy findings

Table XI. Factors influencing the development of RDS in our study population.

	RDS (n = 38)	no-RDS (n = 131)	P
Gestational age at delivery mean ± S.D. (days)	222 ± 19	233 ± 14	< 0.005
Birth weight mean ± S.D. (g)	1636 ± 522	2041 ± 504	< 0.001
Gestational age at treatment mean ± S.D. (days)	210 ± 14	219.0 ± 13	< 0.005
Treatment to delivery time mean ± S.D. (days)	12 ± 13	13 ± 15	> 0.05
ROM to delivery time mean ± S.D. (hours)	63 ± 118	57 ± 151	> 0.05
Use of betamimetics (%)	92	88	> 0.05
Cesarean section (%)	45	41	> 0.05
Male sex (%)	49	54	> 0.05
Placenta previa (%)	8	2	> 0.05
Apgar 1′ (mean ± S.D.)	3.5 ± 2.0	6.4 ± 2.6	< 0.001
Apgar 5′ (mean ± S.D.)	5.9 ± 1.7	7.6 ± 1.9	< 0.001
Ambroxol treatment (%)	29	55	< 0.005

4 Discussion

The fact that none of the substances alleged to increase surfactant production has yet been accepted as a true alternative to steroids for prevention of RDS is probably due to the difficulty of correct clinical evaluation of their efficacy. There are few other cases of drug efficacy assessment in which the final effect – in the present instance the lowering of the incidence of RDS – can be influenced by such a large number of different factors, of which those currently known are:
1) gestational age at delivery, 2) birth weight, 3) gestational age at treatment, 4) treatment to delivery time, 5) ROM to delivery time, 6) mode of delivery, 7) neonatal condition at birth, 8) sex of the newborn, 9) race of the newborn, 10) use of beta-mimetic tocolytic agents, 11) twin births, 12) fetal levels of PRL, T3 and T4, 13) maternal smoking habits, 14) obstetric abnormalities including placenta previa, diabetes, Rh immunization, hypertension.

If to these is added the difficulty of extrapolating animal model data to humans, it becomes clear that any assessment of the efficacy of a drug for RDS prevention must necessarily be made by means of multiple randomized human trials in which the principal interfering factors are either excluded or homogeneously distributed among the groups studied. Such trials should also be multicenter in nature, so as to reduce the effect of variety in the quality of prenatal care.

Our study has certain limitations, mainly due to the fact that it is not blinded, even if non-excluded interference factors were homogeneously distributed between the two groups.

Moreover, the percentage of low birth weight infants was slightly, though not significantly, higher in the betamethasone group, even if ambroxol was significantly more effective than betamethasone in infants born before the 31st week.

Our incidence of RDS was rather high, compared with that reported by others [1, 4, 7, 14] and this was probably due to the fact that we also considered all cases of mild RDS. We consider noteworthy that in the ambroxol group the incidence of RDS was significantly lower in the severe cases taken alone where a diagnostic error is less probable.

Thus, although clearly our results are by no means conclusive, they suggest that ambroxol is at least as effective as the steroids for prevention of RDS and is effective also in cases steroids are not, such as twin delivery, ROM more than 48 hours prior to delivery, female sex.

Despite several experimental data demonstrating its effectiveness in stimulating surfactant production, this drug had found only a some-

what limited use for RDS prevention, mainly because the usual dosage regimen (1 g/day for 5 days) is too long for cases of threatened premature delivery, especially if there is concomitant ROM, as confirmed by the high percentage of cases that did not complete the total dosage regimen in our trial too.

With a view to concluding clinical trials with this substance, we had already successfully checked that it significantly modified the palmitic acid/stearic acid (P/S) ratio in amniotic fluid, as compared with a placebo [9], using the more time intensive dosage regimen in which 4 g were administered in 36 hours. This same regimen was available in this trial and gave better results than the long dosage regimen, although the difference was not significant.

The higher incidence of bacterial and micotic infections in the infants of the betamethasone group can be related to the findings of LAZZARIN [6], showing a significant defect of PMNL activity and a significant decrease of OKT4+ cells (currently considered as T-helpers), in 10 preterm infants of the betamethasone group as compared either with 10 preterm infants of the ambroxol group or 10 preterm infants born to non-treated mothers or 10 healthy term infants. The damage to immunocompetent cell functions might be the cause of the higher infection rate in steroid treated infants and warrants great caution in the use of immunosuppressor drugs in preterm newborns, which are already susceptible to a high incidence of infectious pathology, due to functional immaturity of cellular immune responsiveness. Our findings suggest that steroids might actually raise the risk of infection in very low birth weight infants and when ROM occurs more than 48 hours before delivery.

In contrast, current knowledge suggests that ambroxol lacks negative maternal, fetal and neonatal side effects. This is a major advantage, indicating this drug as a valid alternative to steroids for prevention of RDS, if its efficacy is confirmed by further studies, also in those patients that were excluded in our trial, because of the presence of a relative counterindication to the use of steroids (hypertension, diabetes).

Since gestational age, birth weight and neonatal well-being were the only decisive factors affecting the development of RDS in our trial, it is apparent that, together with maternal administration of ambroxol, adequate tocolysis and good prenatal care assure the most favorable modes of delivery to preterm infants.

Summary

The results are reported of a multicenter randomized study of the effectiveness of maternal administration of betamethasone versus ambroxol, a substance of the group of the benzylamines, for prevention of RDS in preterm infants.

Women of 27 to 34 weeks gestation with threatened premature delivery or planned premature delivery were admitted to the trial. Between September 1981 and November 1984 a total of 288 randomized patients delivered 315 neonates. The incidence of RDS was assessed in 169 viable neonates born before the 37th week.

Of these 86 were born of 76 mothers treated with betamethasone and 83 of 76 mothers treated with ambroxol. The overall incidence of RDS was significantly ($P < 0.05$) higher in the betamethasone group (31%) than the ambroxol group (13%). Ambroxol was significantly more effective than betamethasone in twin births, in infants born before the 31st week, when ROM to delivery time was more than 48 hours, when treatment to delivery time was between 2 and 7 days and in female infants.

The neonatal infection rate was significantly higher ($P < 0.05$) in the group of betamethasone treated infants (18% with four fatalities) than in the group of ambroxol treated infants (9% with one fatality).

These results suggest that ambroxol may be a valid alternative to steroids for prevention of RDS.

Keywords: Lung maturity, respiratory distress syndrome (RDS), surfactant.

Zusammenfassung

Vergleich von Ambroxol und Betamethason zur Prävention des RDS — eine multizentrische kontrollierte Studie

Es werden die Ergebnisse einer multizentrischen randomisierten Studie vorgestellt, in der die Wirksamkeit von Betamethason bzw. Ambroxol, eine Substanz aus der Gruppe der Benzylamine, zur Prävention eines RDS bei Frühgeborenen miteinander verglichen wurde.

In die Studie aufgenommen wurden Frauen von der 27. bis 34. Schwangerschaftswoche mit drohender Frühgeburt bzw. geplanter vorzeitiger Entbindung. Zwischen September 1981 und November 1984 wurde ein Kollektiv von 288 randomisierten Patienten zusammengestellt, die von insgesamt 315 Neugeborenen entbunden worden waren. Bei 169 lebenden Kindern vor der 37. Woche wurde ein RDS diagnostiziert. 86 dieser Kinder waren aus der Gruppe von 76 Müttern, die mit Betamethason behandelt worden waren, 83 aus der Gruppe von 76 Müttern, die Ambroxol erhalten hatten. In der Betamethason-Gruppe war die Inzidenz eines RDS signifikant höher ($p < 0.05$) als in der Ambroxolgruppe (31% versus 13%).

Bei Zwillingsgeburten, bei Kindern vor der 31. Woche, bei länger als 48 h zurückliegendem Blasensprung, bei einem Zeitraum von 2 bis 7 Tagen von Behandlungsbeginn bis zur Entbindung und bei weiblichen Neugeborenen war Ambroxol signifikant wirksamer als Betamethason.

Die neonatale Infektionsrate war in der Betamethason-Gruppe signifikant höher als in der Ambroxol-Gruppe ($p < 0.05$; 18% mit 4 Todesfällen versus 9% mit einem Todesfall).

Unsere Ergebnisse zeigen, daß bei der Prävention des RDS Ambroxol eine echte Alternative zu den Steroiden sein kann.

Schlüsselwörter: Lungenreife, respiratorisches Distress-Syndrom (RDS), Surfactant.

Résumé

Une alternative aux steroïdes pour la prévention du syndrome de détresse respiratoire (SDR): étude multicentrique avec groupe controle comparant ambroxol versus bétaméthasone

On rapporte les résultats d'une étude multicentrique randomisée de l'efficacité de la prise maternelle de bétaméthasone versus ambroxol, substance du groupe des benzylamines, dans la prévention du SDR chez les enfants prématurés.

Sont entrées dans l'essai les femmes de 27 à 34 semaines de gestation avec une menace d'accouchement prématuré ou un accouchement prématuré programmé. Entre septembre 1981 et novembre 1984, 288 patientes randomisées, au total, ont donné naissance à 315 nouveaux-nés. On a estimé l'incidence du SDR à 169 nouveaux-nés viables nés avant la 37ème semaine. Parmi ceux-ci 86 sont nés de 76 mères traitées par bétaméthasone et 83 de 76 mères traitées par ambroxol. L'incidence globale du SDR a été de façon significative ($p < 0,05$) plus élevée dans le groupe avec bétaméthasone (31%) que dans le groupe avec ambroxol (13%).

L'ambroxol est plus efficace de façon significative que la bétaméthasone chez les jumeaux, chez les enfants nés avant la 31ème semaine, lorsque l'intervalle entre l'ouverture de l'œuf et l'accouchement était supérieur à 48 heures, lorsque le délai entre le traitement et l'accouchement était compris entre 2 et 7 jours, et chez les enfants de sexe féminin.

Le taux d'infections néonatales a été de façon significative ($p < 0,05$) plus élevé dans le groupe des enfants traités par bétaméthasone (18% avec 4 décès) que dans le groupe des enfants traités par ambroxol (9% avec 1 seul décès).

Ces résultats suggèrent que l'ambroxol peut représenter une alternative valable aux stéroïdes dans la prévention du SDR.

Mots-clés: Maturité pulmonaire, surfactant, syndrome de détresse respiratoire (SDR).

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